The Pending Claims

Claims 1, 3, 4 and 13-23 are currently pending and are directed to a method of treating cancer.

Amendments to the Claims

Claims 1 and 13 were amended so as to not unduly limit the scope of the claims. The amendment of claims 1 and 13 is supported by the claims as originally filed. Therefore, no new matter has been added by way of these amendments.

The Office Action

Claims 1, 3, 4, 13-15 and 20-23 were rejected under 35 U.S.C. § 103 as obvious in view of and, therefore, unpatentable over (i) Rao et al. or Tso et al. as defined in footnotes 18 and 20 of Wu et al. or (ii) Qian or Kim et al. as set forth in lines 11-15 of page 1 of the instant application. Claims 1, 3, 4, 13-16 and 20-22 were rejected under 35 U.S.C. § 103 as obvious in view of and, therefore, unpatentable over Band et al. Claims 1, 3, 5, 13-16 and 20-23 were rejected under 35 U.S.C. § 112, first paragraph. Claims 17-19 were withdrawn from further consideration by the Office as being drawn to a non-elected invention. Reconsideration of these rejections and the withdrawal of claims 17-19 from further consideration is hereby requested.

Discussion of Withdrawal of Claims 17-19 from Consideration

The Office withdrew claims 17-19 from further consideration as drawn to a nonelected invention. Applicants respectfully submit that the Office's request for cancellation of claims 17-19 is not warranted.

The restriction requirement and requirement for election of species of September 18, 1995, set forth a two-way restriction requirement. Claims 1, 3 and 4, which are directed to the use of gossypol, gossypolone, and pharmaceutically acceptable salts thereof, were grouped into Group I. Claims 9-12, which are directed to the use of such compounds in further combination with other chemotherapeutic agents, were grouped into Group II. In addition to the requirement for restriction, Applicants were required to elect a species, i.e., choose a specific compound, for purposes of examination. Applicants elected Group I and gossypol. Claim 1 is a generic claim that recites gossypol, gossypolone and pharmaceutically acceptable salts thereof. Claims 17-19 depend from generic claim 1.

The Office's request for cancellation of claims 17-19 at this time is believed to be improper. Under M.P.E.P. § 809.02(c), only when a generic claim has been found to be allowable and the claims to the nonelected species do not depend from, or otherwise include all of the limitations of, an allowed generic claim (as required by 37 C.F.R. § 1.41) is cancellation of claims to nonelected species proper. Here, the generic claim has not yet been found allowable. Furthermore, the claims that the Examiner has withdrawn from consideration,

namely claims 17-19, depend from the generic claim. Accordingly, in the event that the generic claim were found to be allowable, it still would be improper to cancel claims 17-19. Accordingly, Applicants request withdrawal of the requirement for cancellation of claims 17-19.

Discussion of Rejections under 35 U.S.C. § 103

Claims 1, 3, 4, 13-15 and 20-23 were rejected under Section 103 as obvious in view of and, therefore, unpatentable over Rao et al., Tso et al., Qian, or Kim et al. According to the Office Action dated March 17, 1997, the cited references disclose that gossypol is an agent that is effective against cancer, including breast cancer, in mammals (i.e., mice). Based on these references, the Office concluded that one of ordinary skill in the art would be motivated to try the instantly claimed method of treating cancer in humans with gossypol, a pharmaceutically acceptable salt of gossypol, gossypolone, a pharmaceutically acceptable salt of gossypolone, or any combination thereof, and that the invention as a whole was, therefore, obvious. The Office Action of February 27, 1998, made final the rejection of the earlier Office Action for the previously cited reasons, and requested a side-by-side comparison of the claimed invention and the prior art.

Claims 1, 3, 4, 13-16 and 20-22 were rejected under Section 103 as obvious in view of and, therefore, unpatentable over Band et al. According to the Office Action of February 27, 1998, the cited reference discloses that (-) gossypol can

be used to treat ovarian cancer cells *in vitro*, and that one of ordinary skill in the art would be motivated to treat these cancer cells in human patients *in vivo*. These rejections are traversed for the reasons set forth below.

Band et al. relates to the ability of gossypol to inhibit the proliferation of cancerous and non-cancerous cells *in vitro*, and to the relative potency of (-) and (+) gossypol in this capacity. According to the reference, each of the cell types studied, including both reproductive and non-reproductive cancer cell lines, and actively proliferating, non-cancerous, untransformed cells, was found to be equally sensitive to gossypol treatment *in vitro*. Band et al., therefore, concludes that "gossypol *in vitro* acts as a general and nonselective antiproliferative agent" (Band et al., page 276, col. 2, through page 277, col. 1, emphasis added).

In other words, Band et al. teaches that gossypol *in vitro* is as lethal to normal, untransformed, non-cancerous cells as it is to cancerous cells. As set forth in the accompanying Rule 1.132 Declaration of Dr. Marcus Reidenberg, "[s]uccessful anticancer drugs selectively kill tumor cells; if anticancer drugs killed cells indiscriminately, the cure would be worse than the disease" (paragraph 5). In view of these facts, Band et al. not only fails to provide one of ordinary skill in the art with the motivation to use gossypol, or any other compound encompassed by the claims, to treat cancer *in vivo*, let alone in a human, Band et al. further fails to provide the artisan of

ordinary skill with a reasonable expectation of successful, i.e., safe and effective, treatment of cancer.

Rao et al. is directed to the use of gossypol for the inhibition of tumors in three murine (i.e., mouse) tumor models. The efficacy of gossypol against these tumors was reported to be either non-existent or highly variable.

For example, gossypol had no inhibitory effect on two types of murine leukemia tumors (L1210 and P388), and the gossypol-treated mice died, on average, at the same time as the untreated mice (i.e., after about 8 days). On the other hand, the administration of gossypol to mice at a reported optimal dose of 0.5 mg/mouse (about 25 mg/kg, based on an average mouse weight of 20 g [0.02 kg] as reported in Rao et al. at p. 20, col. 2) two days after inoculation with adenocarcinoma cells (CA 755) reportedly resulted in 66% of the mice being free of visible tumors after 100 days, with the remaining mice dying from the effects of tumors in an average of 18 days.

However, when gossypol was administered at a dosage outside a very narrow optimal range, its efficacy against adenocarcinoma plummeted. When the dosage was increased to 1.2 times the optimum (to 0.6 mg/mouse, about 30 mg/kg), 60% of the mice died due to the toxicity of gossypol (Rao et al., page 24, col. 1 at lines 15-17). When the dosage was decreased to 0.8 times the optimal dosage (to 0.4 mg/mouse, about 20 mg/kg), the long-term (>100 days) survival rate was cut by more than half, from 66% to 30%, and when the mice were administered two separate doses of gossypol at 0.6 times the optimal dosage

(i.e., two doses of 0.3 mg/mouse, about 15 mg/kg, administered two and four days following inoculation), the long-term survival rate decreased to 0%. In other words, at dosages slightly below the optimal therapeutic dosage, gossypol was not an effective tumor inhibitor, and the mice died from the effects of the tumors, while at dosages slightly above the optimal therapeutic dosage, gossypol, itself, was lethal.

In view of the *in vitro* toxicity of gossypol to cancerous and noncancerous human cells alike as reported by Band et al., one of ordinary skill in the art, upon reading Rao et al., would reasonably conclude that gossypol would be toxic to cancerous and noncancerous human cells *in vivo* (see Declaration, para. 6). Therefore, one of ordinary skill would not even be motivated to try gossypol or any other compound encompassed by the claims in the treatment of human cancer, let alone reasonably expect that such compounds would be safe and effective anti-cancer drugs (see Declaration, para. 9).

In fact, Rao et al. concludes that "gossypol does not appear to be a promising antitumor agent" (Rao et al., p. 24, bottom of col. 2), and thereby clearly teaches away from the use of gossypol in a method of treating cancer in a human. It is well known that when a reference teaches away from an invention, its power of suggestion and ability to provide motivation are diminished.

Tso is directed to mice inoculated with Ehrlich ascites tumor cells, which do not even occur in humans. However, the results of Tso are consistent with the findings of Rao et al.,

in that gossypol could be safely and effectively administered to mice only within a very narrow dosage range. According to Tso, when gossypol was administered to mice at a daily dosage of 25-100 μg (about 0.7-2.7 mg/kg/day, based on an average mouse weight of 37 grams, as reported on page 260 of Tso), the lifespan of the mice was extended by an average of about 3 to 4 days compared to untreated mice. However, when the dosage was increased to 250 μg per mouse (about 7 mg/kg/day), which is only 2.5 times higher than the optimal therapeutic dosage of 100 μg/mouse (Tso, SUMMARY, lines 4-5), gossypol was extremely toxic, and the average lifespan of the treated mice was as short as the average lifespan of the untreated mice. In other words, and in analogy to Rao et al., gossypol was lethal at dosages only 2.5 times higher than the reported optimal therapeutic dosage.

In view of the *in vitro* toxicity of gossypol to both cancerous and noncancerous cells as reported by Band et al., alone or in further view of the lethal toxicity of gossypol *in vivo* as reported by Rao et al., one of ordinary skill in the art, upon also reading Tso, would still reasonably conclude that gossypol would be toxic to both cancerous and noncancerous human cells *in vivo* (see Declaration, para. 9). Therefore, an ordinary artisan still would not even be motivated to try gossypol or any other compound encompassed by the claims in the treatment of human cancer, let alone reasonably expect that such compounds would be safe and effective anti-cancer drugs (see Declaration, para. 9).

In fact, Tso concludes that gossypol is a compound whose "applicability as an anti-tumor drug is still limited" (Tso reference, p. 259-260), and thereby clearly teaches away from the use of gossypol in a method of treating cancer in a human. As previously mentioned, it is well known that when a reference teaches away from an invention, its power of suggestion and ability to provide motivation are diminished.

Therefore, in view of the above, and as pointed out in the instant specification at, for example, page 4, line 25, through page 5, line 4, it is surprising and unexpected that Applicants have discovered that gossypol and related compounds are safe and effective in treating cancer in humans. As pointed out in paragraph 9 of the Declaration, at the time that the present invention was made, one of ordinary skill in the art would not have believed that it would have been possible to determine successfully a safe and effective dosage range in genetically heterogeneous humans for a drug that displays such a general toxic effect *in vitro*, and such a narrow window of efficacy and safety in a genetically homogenous population of in-bred rodents. Moreover, neither Rao et al. nor Tso teaches or suggests the blood levels, dosages, or routes of administration of gossypol, gossypolone, and physiologically acceptable salts thereof, alone or in various combinations, as taught (for example, in Table 4) and claimed in the instant application.

Based on the foregoing, it is evident that the Office has failed to establish a *prima facie* case of obviousness. It is well-known that to establish a *prima facie* case, the Office

must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time that the invention was made. Lastly, the prior art reference or combination of references must teach or suggest all of the limitations of the claims. Here, the Office has failed to satisfy even one of the three requirements with respect to any of the cited references. Therefore, for the Office to request a side-by-side comparison with the cited references is not warranted and, for the sake of argument, even if such a side-by-side comparison were warranted, Applicants have demonstrated surprising and unexpected results.

Qian and Kim et al., on the other hand, do not even relate to the treatment of cancer. Rather, they are directed to the spermicidal effects of gossypol. Accordingly, an artisan of ordinary skill could not and would not be motivated to modify the teachings of either of these references in order to treat cancer in a human as claimed. Moreover, these references could not possibly provide an artisan of ordinary skill with a reasonable expectation of success, nor do they meet the limitations of the claims, as they do not even relate to cancer in any form. In this regard, to the extent that Qian and Kim

et al. show that gossypol kills noncancerous human cells, Qian and Kim et al., like Band et al., fail to motivate the ordinary artisan to use gossypol or any other compound encompassed by the claims in the treatment of cancer in humans, let alone to reasonably expect that such compounds would be safe and effective anti-cancer drugs.

Therefore, Applicants submit that claims 1, 3, 4, 13-16 and 20-23 are not obvious in view of and, therefore, are patentable over Band et al., Rao et al., Tso, Qian and Kim et al., alone or in any combination. Accordingly, Applicants request withdrawal of these rejections.

Discussion of Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 5, 13-16 and 20-23 were rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action, the blood concentration range set forth in the rejected claims, 200-1000 ng/dl, was described in the specification only for the (-) isomer of gossypol. As a result, the Office contends that it would not be reasonably conveyed to a person skilled in the art that the inventors had possession of blood concentrations in the range of 200-1000 ng/dl for gossypol, a pharmaceutically acceptable salt of gossypol, gossypolone, a pharmaceutically acceptable salt of gossypolone, or any combination thereof, as claimed. This rejection is traversed for the reasons set forth below.

In view of the amendment of claims 1 and 13, this rejection is believed to be moot with respect to claims 1, 3,

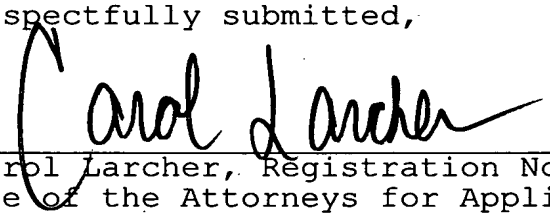
5, 14, 15 and 21-23. Claims 16 and 20, which depend from claims 1 and 13, respectively, are directed to blood levels of gossypol, a physiologically acceptable salt of gossypol, gossypolone or a physiologically acceptable salt of gossypolone of from about 400 to about 1000 ng/dl. These blood levels are explicitly recited for each of these compounds at page 15 of the specification. Accordingly, Applicants request withdrawal of this rejection.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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